-- The activities of the mouse IL-1α, IL-1β, and IL-1γ have been compared as to their ability to induce IFN-γ, alone or in combination with IL-2 or IL-12 in SCID splenocytes and purified NK cells. See Hunter, et al. (1995) J. Immunol. 155:4347-4354; and Bancroft, et al. (1991) Immunol. Revs. 124:5-24 [xxx]. The IL-1γ was found to be much more potent in stimulating IFN-1γ than either IL-1α or IL-1β. IL-1δ and IL-1ε and their agonists or antagonists should have related activities, typically affecting similar immune functions, including inflammatory responses.--

C1

IN THE CLAIMS

Please cancel claim 10 without prejudice to subsequent renewal or future prosecution. Please amend the claims as follows. A clean version of all pending claims is shown in the attached Appendix.

25. (Amended) The binding compound of claim 24, wherein said 12 consecutive amino acid segment is selected from:

(1) LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsn-Asn;
(2) IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIle-LeuGlyValGln;
(3) SerProValIleLeuGlyValGlnGlyGlySerGlnCys;
(4) ProIleLeuLysLeuGluProValAsnIleMetGluLeu;
(5) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe;
(6) PheLeuCysThrSerProGluAlaAspGlnProVal; or
(7) ThrGlnIleProGluAspProAlaTrpAspAlaProIle [; or
(8) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe].

REMARKS

Status of the Application and the Present Response

Claims 7-10 and 20-25 are pending and stand rejected in the application. With entry of the present Response, claim 10 has been canceled without prejudice, and claim 25 has

been amended to delete redundant claim language. No new matter has been added by the present amendments and submissions.

The following remarks address issues raised in the Office Action.

Objection to the Specification

The Office Action raised objection to the specification because the specification allegedly contains an embedded hyperlink and/or other form of browser-executable code. Upon reviewing the specification as filed, Applicant could not find any executable hyperlink or other browser-executable code in the specification. Applicant notes that there is only one non-active URL site in the text of the specification, i.e., at page 28, line 34. However, such is not an "embedded hyperlink" prohibited by the MPEP. Rather, the MPEP only prohibits active browser-executable links. The MPEP specifically states that "examiners should not object to these hyperlinks" that are not intended to be active by applicants (see, e.g., § 608.01(a) of the MPEP, 8th ed., August 2001, at page 600-60, the paragraph bridging the left and right columns). If this objection is maintained, clarification is respectfully requested.

The specification was also objected to because of incomplete citation of a publication on page 31. In response, Applicants have amended the specification to insert the omitted information.

Objection to Claims

Claim 25 was objected to because it contains redundant claim language. With entry of the instant Response, the claim has been amended to correct the redundancy.

Rejections under 35 U.S.C. 101 and 35 U.S.C. 112, 1st Paragraph

The instant Office Action maintained the rejection of the pending claims as allegedly lacking apparent or disclosed patentable utility. The Office Action maintained that the disclosed utilities cannot be accepted without supporting evidence, and that protein function cannot be predicted based solely on structural similarity. The Examiner invited Applicants to submit evidence in the form of declaration or post-filing publications that support utilities disclosed in the specification. Applicants respectfully traverse the instant rejection for the reasons stated below.

1. Standard for patentable utility requirement

Applicant notes that, according to the MPEP (§ 2107.02 III-A), a disclosed utility corresponding to the claimed subject matter satisfies the utility requirement under § 101 absent evidence which would cast doubt on the objective truth of the disclosed utility. There is no legal requirement that the disclosed utility must be supported by conclusive experimental results. The MPEP has noted that several judicial decisions "direct the office to presume that a statement of utility made by an applicant is true." As quoted in the MPEP:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. [MPEP § 2107.02-III-A; quoting *In re Langer*, 503 F.2d 1380 (CCPA 1980), at 1391; emphasis original]

The MPEP has also cautioned that "office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical filed of the invention or for other general reasons" (emphasis added). Rather, "any inquiry must start by asking if there is any reason to question the truth of the statement of utility" (MPEP § 2107.02-III-A; at page 2100-39).

The MPEP specifically noted that "applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt'" and that "nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty." See, MPEP § 2107.02-VII. The MPEP further states that "evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true" (MPEP § 2107.02-VII; emphasis original).

In addition, with respect to the "credible" prong of the utility requirement, the MPEP states that the determination is "whether the assertion of utility is believable to a person of ordinary skilled in the art based on the totality of evidence and reasoning provided." The MPEP further notes that "an assertion is credible unless (A) the logic underlying the assertion

is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion" (MPEP § 2107.02-III-B).

Further, Applicant notes that, as stated in the MPEP, "an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not credible," do not render the claimed invention lacking in utility" (MPEP § 2107.02-I; at page 2100-37; emphasis added).

2. Disclosed utilities and post-filing supporting evidence

The present inventors discovered that IL-1δ is a novel member of the IL-1 family. Members of the IL-1 family are involved in inflammation, infectious response, and other immunological disorders (see, Debets et al., J. Immunol. 167:1440-1446, 2001; at page 1440, left column). Structurally, they share a common β-barrel structure which is formed by twelve β-strands (see, Kumar et al., J. Biol. Chem. 275:10308-10314, 2000; at page 10308, left column).

The subject specification disclosed that IL-1δ has the conserved barrel structure seen in the other IL-1 family members (see, e.g., Fig. 1B; and Table 2 at page 22). Sequence homology between IL-1δ and the other IL-1 cytokines (e.g., IL-1α and IL-1β) also indicates that IL-1δ belongs to the IL-1 family (see, pages 13-22). A number of post-filing publications confirmed that IL-1δ indeed belong to the IL-1 family. For example, Kumar et al., *supra*, described a IL-1 family member, IL-1H1, which has sequence that is essentially the same as that of IL-1δ. Taylor et al. (Genomics 79:726-733, 2002) and Nicklin et al. (Genomics 79:718-725, 2002) reported genomic organization of the IL-1 locus which includes IL-1F5, another terminology that has been used in the art for IL-1δ.

Functionally, the subject specification disclosed that IL-1δ can play a role in inflammatory responses and viral infection (see, e.g., page 31; and page 79, lines 7-28). These disclosed utilities were confirmed in Kumar, et al. (*supra*). In this publication, it was demonstrated that IL-1H1 expression was observed in herpes simplex virus infection (page 10313, right column, middle paragraph). The authors noted that "since viral infection results in significant inflammation and necrosis, it is possible that IL-1H1 expressed and released during this process may contribute to the inflammation" and that "IL-1H1 may play a role in viral clearance and/or repair processes" (the paragraph bridging pages 10313 and 10314).

Similarly, Debets et al., *supra*, showed that IL-1δ expression is upregulated in psoriasis, an chronic inflammatory skin condition. This report also showed that IL-1δ is highly expressed in tissues containing epithelial cells such as lung, consistent with the subject disclosure (see, e.g., page 95, lines 33-34).

Thus, the subject specification taught that IL-1δ can play a role in inflammation and a number of other cellular activities (see, pages 79-80). These are precisely what were experimentally confirmed in the published reports (e.g., Kumar et al. and Debets et al.).

3. Analysis of the instant rejection

(i) Substantial, specific, and credible utilities

Applying the above-noted legal standard for utility requirement, there is no doubt that the subject specification has disclosed patentable utilities that are substantial. Chromosomal mapping of IL-1δ gene loci and tissue distribution of IL-1δ expression were disclosed in the subject specification (pages 93-95 and 99). The specification disclosed extensively the structural similarities between IL-1δ and other cytokines of the IL-1 family (e.g., pages 31 and 40). Based on structural comparison, the specification disclosed that IL-1δ can bind to IL-1 receptor (page 42, lines 7-10 and 35-36), and that IL-1δ can have IL-1 receptor antagonist activity (pages 41-42). The specification also disclosed that IL-1δ could participate in inflammation and other immunological disorders (pages 31 and 79-80). The specification further disclosed that IL-1δ can be useful in identifying novel receptors that are involved in IL-1 related immune response and taught how to identify such receptors (page 101). Such utilities are certainly ***substantial*** because they define ***real world*** uses of the claimed subject matter.

Utilities of the subject invention are also specific. As stated in the MPEP, a "specific utility" is specific to the subject matter claimed, which is contrasted with a general utility that would be applicable to a broad class of the invention. The MPEP further explains that non-specific utility exists in "situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful." The examples noted by the MPEP as non-specific utility include "indicating that a compound may be useful in treating unspecified disorders, or that the compound has non-specified 'useful biological properties.'" Similarly, a polynucleotide whose use is disclosed simply as gene

probe or chromosome marker would not be considered to be specific. See, MPEP § 2107.01-I, at page 2100-32).

By contrast, IL-1δ has specific utilities including its role in modulating various cellular responses (e.g., inflammation) and its use in screening for novel IL-1 receptors. In addition, the specification set forth other utilities of the presently claimed invention. For example, IL-1δ binding compounds can have diagnostic or therapeutic applications, e.g., in modulating interleukin mediated responses (page 68, lines 19-29). The specification also disclosed how to assay expression level of IL-1δ in various human and mouse cell types (see, e.g., page 95, lines 11-27). The specification further taught that IL-1δ sequences can be used for detecting levels of IL-1δ in patients suspected of having an immunological disorder (page 77, line 29-33). It is readily clear that not all novel polypeptides and antibodies thereto would have such utilities. Rather, these disclosed utilities are ***specific*** because they are specific to the subject matter being claimed (e.g., activities mediated by members of the IL-1 family). They are clearly distinguished over the above-noted non-specific utilities exemplified in the MPEP.

Finally, the disclosed utilities are also ***credible***. First, the subject disclosures as well as knowledge known to the skilled artisans are more than sufficient to satisfy the "more likely than not true" test. In addition, as discussed above, some of the disclosed utilities of the subject invention were experimentally confirmed by peer reviewed publications. These publications demonstrated that IL-1δ indeed plays a role in inflammatory responses. This strongly indicates that the utilities as disclosed in the subject invention would have been regarded as credible by the skilled artisans.

(ii) References cited by the Examiner

The instant rejection was maintained partially in view of the following references cited by the Examiner, Murdoch et al. (Blood 95:3032-43, 2000), Ji et al. (J. Biol. Chem 273:17299-302, 1998), Tischer et al. (U.S. Patent No. 5,194,596), Vukicevic et al. (Proc. Natl. Acad. Sci. USA 93:9021-26, 1996), and Massague et al. (Cell 49:437-8, 1987). These references allegedly illustrate functional diversity among cytokines or growth factor families despite close structural similarities. Applicants respectfully note that these references at most suggest that structurally related members of some specific cytokine families may not share conserved functional properties. They do not indicate that, as a general rule, conserved

functional properties are not present in members of other cytokine families (e.g., the IL-1 family).

Similarly, the Examiner also cited a few other references in maintaining the instant rejection, Skolnick et al. (Trends in Viotech. 18:34-39), Bork et al. (Cur. Opin. Struc. Biol. 8:331-332, 1998), and Brenner et al. (Trends in Genetics 15:132-33; 1999). It was alleged that these references indicate that amino acid sequence homology cannot necessarily predict the function of proteins. However, these references relate to the general technical fields of molecular biology and biochemistry, not specific to the subject matter of the present invention. The cited art at most suggested that homology-based functional predictions may not always be accurate. By no means did these references establish that in any given case, sequence homology based functional prediction cannot be "more likely than not true."

In summary, the cited references are clearly not evidence that the logic underlying the asserted utilities of the present invention is seriously flawed or that the facts upon which the asserted utilities are based are inconsistent with the logic underlying the assertion. As noted above, the MPEP has specifically repudiated the practice of rendering a utility rejection merely based on knowledge in the general technical field of an invention. Applicants respectfully submit that the present invention has disclosed patentable utilities that are substantial, specific, and credible. Withdrawal of the instant rejections is therefore requested.

Additional Rejections

Claim 7 was rejected as allegedly not enabled. The Office Action asserted that the specification did not teach how to use binding compounds that bind at least 8 contiguous amino acids of SEQ ID NO: 2. Applicants respectfully traverse.

It was asserted in the Office Action that the specification did not teach or suggest how to use binding compounds that bind sequences other than those from SEQ ID NO:2. In response, Applicants note that the subject specification taught that fragments of the disclosed sequences can be used as immunogens to generate antibodies (page 61, lines 20-23). Methods of producing antibodies using polypeptides as immunogens are well known in the art (see, e.g., the specification, at page 62).

In addition, the subject specification enabled synthesis of IL-1δ peptides encompassed by claim 7 (i.e., polypeptides comprising at least 8 contiguous amino acids of SEQ ID NO:2). These peptides all derive their sequences from the disclosed sequence. Thus, although the specification did not enumerate the amino acid sequence of each possible peptide encompassed by the claim, the sequences of these polypeptides are all necessarily described in the sequence listing. It is acknowledge that the number of such peptides may be large. However, it does not follow that production of such peptides are not enabled by the subject disclosure. Rather, there would be no undue experimentation for a skilled artisan to generate such peptides from the disclosed sequence (i.e., SEQ ID NO:2).

Further, the specification also enabled production of antibodies against IL-1δ peptides comprising at least 8 contiguous amino acids of SEQ ID NO:2. The use of peptides as immunogens for antibody production is well known and routinely practiced in the art. Harlow and Lane (Antibodies: A Laboratory Manual, 1988) states:

> Peptide-carrier conjugates seldom fail to elicit a response because of tolerance. Consequently, the peptides can usually be seen as epitopes, and high-titered antisera commonly prepared.
> . . .
> The two most important advantages of anti-peptide antibodies are that they can be prepared immediately after determining the amino acid sequence of a protein (either from protein sequencing or from DNA sequencing) and that particular regions of a protein can be targeted specifically for antibody production." [at page 73; emphasis added; copy attached]

Moreover, knowledge of how to choose appropriate peptide sequences for antibody production is also well known in the art (see, e.g., Harlow and Lane, supra, at pages 75-76; copy attached). Thus, the subject specification and knowledge well known in the art enable synthesis of IL-1δ peptides comprising at least 8 contiguous amino acids of SEQ ID NO: 2, as well as production of anti-peptide antibodies using such IL-1δ peptides. Therefore, the subject invention as recited in claim 7 is clearly enabled.

Claim 10 was rejected as not enabled because no nexus between any particular disease and an alteration in IL-1δ level was provided in the specification. Although Applicants respectfully traverse this rejection, to expedite prosecution of the subject application, Applicants have canceled claim 10. The rejection is therefore moot.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Hugh Wang
Reg. No. 47,163

Attachments:

Clean version of amendments;
Pages 72-73 and 75-76 of Harlow and Lane (Antibodies: A Laboratory Manual, 1988);
Debets et al., J. Immunol. 167:1440-1446, 2001;
Kumar et al., J. Biol. Chem. 275:10308-10314, 2000;
Taylor et al., Genomics 79:726-733, 2002;
Nicklin et al., Genomics 79:718-725, 2002

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Appendix: Clean Version Of Amendments

I. Amendments to the Specification

1. At page 3, please replace the paragraph starting at line 17 with the following replacement paragraph.

-- The activities of the mouse IL-1α, IL-1β, and IL-1γ have been compared as to their ability to induce IFN-γ, alone or in combination with IL-2 or IL-12 in SCID splenocytes and purified NK cells. See Hunter, et al. (1995) J. Immunol. 155:4347-4354; and Bancroft, et al. (1991) Immunol. Revs. 124:5-24. The IL-1γ was found to be much more potent in stimulating IFN-1γ than either IL-1α or IL-1β. IL-1δ and IL-1ε and their agonists or antagonists should have related activities, typically affecting similar immune functions, including inflammatory responses.--

II. Amendments to the Claims (claims unamended herewith appear in small font)

7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from SEQ ID NO: 2.

8. The binding compound of Claim 7, wherein said binding compound is an Fv, Fab, or Fab2 fragment.

9. A kit comprising said binding compound of Claim 7, and:

a) a compartment comprising said binding compound; and/or

b) instructions for use or disposal of reagents in said kit.

20. A method of:

A) making an antiserum comprising an antibody of Claim 7, comprising immunizing a mammal with an immunogenic amount of a peptide comprising a 12 consecutive amino acid segment of SEQ ID NO: 2; thereby causing said antiserum to be produced; or

B) producing an antigen:antibody complex, comprising contacting a rodent IL-1δ protein or peptide with a binding compound of Claim 7; thereby allowing said complex to form.

21. The binding compound of Claim 7, wherein said antibody is a polyclonal antibody.

22. The binding compound of Claim 7, wherein said antibody is detectably labeled.

23. The binding compound of claim 7, wherein said at least 8 contiguous amino acid residues of SEQ ID NO:2 is selected from the group consisting of residues 8-24; 27-48; 56-73; 77-106; 108-125; 130-156; and 74-98.

24. The binding compound of claim 7, wherein said polypeptide comprises at least 12 contiguous amino acid residues from SEQ ID NO: 2.

25. The binding compound of claim 24, wherein said 12 consecutive amino acid segment is selected from:

(1) LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsn-Asn;
(2) IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIle-LeuGlyValGln;
(3) SerProValIleLeuGlyValGlnGlyGlySerGlnCys;
(4) ProIleLeuLysLeuGluProValAsnIleMetGluLeu;
(5) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe;
(6) PheLeuCysThrSerProGluAlaAspGlnProVal; or
(7) ThrGlnIleProGluAspProAlaTrpAspAlaProIle.